#12 V.6 A/E/dJ 7 GP 1624

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Rudolf Eckardt et al.

GAU 1624
Examiner: T. McKenzie

Serial No. 09/447,490

Filed on 11/23/99

For A PROCESS FOR PRODUCING CARBAMAZEPINE

Attorney's Docket 0691-018a

Box Appeal
Hon. Commissioner of Patents and Trademarks
Washington DC 20231

Sir:

BRIEF ON APPEAL

This Brief on Appeal is enclosed in triplicate, together with a check in the amount of $560 (comprising $300 for the brief fee and $260 for the hearing fee). A hearing is requested. An appeal conference is also requested.

The claims on appeal are included in the appendix to this brief. The presentation of this application is following an earlier appeal after which the claims were amended in the sense that they now require that **acetic acid is the only acid that is present in the claimed process**.

The present invention is a process for producing carbamazepine in a single step by reacting an alkali cyanate in the presence of acetic acid (which is the sole acid), with iminostilbene. The reaction produces carbamazepine, without any need for special protective measures against toxic gases, and with an excellent yield in the order of 98%.

The claims were rejected over **claims** 1, 2 and 14 of European patent No. 277,095, hereinafter referred to as Acklin et al. The rejection **is not based on** the disclosure of Acklin et al., **nor is it based on** U.S. patent No.4,847,374, the US counterpart of Acklin et al. This is an entirely different rejection than on which the earlier appeal was predicated.

The claims of Acklin et al. on which the rejection is based, read in translation:

"1. A process for producing of N, N-(dibenzohexatriethylene) ureas, characterized in that reacting a corresponding N, N-(dibenzohexatriethylene) amine with cyanic acid).

2. A process according to claim 1, characterized in that the reaction is carried out in an organic solvent or mixture of organic solvents in the presence of an acidic agent.

14. A process according to claims 2-4 and 8, characterized in that the acidic agent and also the solvent is acetic acid."

The examiner has entirely ignored the fact that was repeatedly emphasized by the applicant, that no cyanic acid (i.e. hydrogen cyanate) is involved in the herein claimed process. There is no cyanic acid present, not only because the claims expressly provide that the sole acid that is present in the herein claimed reaction is acetic acid, but also, because cyanic acid is a highly toxic gas, and therefore any reaction in which it is involved has to be carried out under special protective conditions against toxic gases, i.e. sealed from the ambient atmosphere. Therefore, the reaction of the claims of Acklin et al. that is relied on for the rejection, is an entirely different reaction between entirely different reaction partners than the reaction claimed in the present invention.

The present invention does not only dispense with the use of the toxic cyanic acid, because no ambient protection is required, but **Acklin et al. actually teaches away** from the possibility of the presence of cyanic acid under the conditions of the herein claimed reaction. Per the teaching of Acklin et al. it is impossible for cyanic acid to be present in the herein claimed reaction. That is because the disclosure of Acklin et al. describes the conditions under which the cyanic acid can be obtained in a first step, before it is used in its claimed reaction as a second step of a two step reaction. In that first step Acklin et al. obtains the cyanic acid by reacting an alkali cyanate with an acid that is a sufficiently strong acid to liberate cyanic acid from, its salts. Acklin et al uses formic acid or an acid that is at least as strong an acid as formic acid, because Acklin et al. teaches that **an acid that is weaker than formic acid, e.g. acetic acid, is not capable of liberating cyanic acid from its salts.** This is the reason that **Acklin et al. actually teaches away from the present invention**, because since in the process of the present invention acetic acid is the sole acid that is employed, and therefore, according to the teaching of Acklin et al. **no cyanic acid <u>can be</u> formed in the presently claimed reaction**.

There is yet further evidence that Acklin et al. does not recognize, or have any bearing on the presently claimed process. Claims 22-24 of Acklin et al. are directed to the two-step process of Acklin et al., rather than only to the second step on which the current rejection is predicated. In claims 22-24 iminostilbene is reacted with an alkali cyanate in the presence of acetic acid. Acklin et al. finds it necessary **also to include a from 5% to 40% excess of sulfuric acid.** This is further clear evidence that Acklin et al. concluded that acetic acid alone is insufficiently strong to produce the cyanic acid which it requires to produce the end product, and a further, a stronger acid such as sulfuric acid, even an excess of sulfuric acid, is also required. The claims on appeal are restricted to acetic acid being the sole acid that is present in the reaction. In the claims on appeal neither cyanic acid, sulfuric acid, nor any other acid outside of the acetic acid is present and all of these unneeded further acids are thus expressly excluded.

Thus the present invention uses an <u>entirely different reaction than that which takes place in Acklin et al.</u>

Consequently, there are "only" two problems with the outstanding rejection, which were **repeatedly** ignored by the examiner:

1.) the reactions in the reference and in the appealed claims are entirely different, because critically different reaction partners are involved, and

2.) the reference teaches the opposite of what is asserted by the examiner as the basis of the rejection.

These facts do not appear to hinder the examiner from maintaining (without any basis in fact or in law) that cyanic acid is used in the reaction of the presently claimed process. In fact, nothing seems to be able to stand in the way of the examiner maintaining the outstanding rejection, be they facts or even the law. The rejection is based entirely on fiction - science fiction.

In carrying forward its line of contradicting the teachings of Acklin et al., the examiner creates some extremely speculative, scientifically sounding theorizing that is entirely unwarranted from, and contradictory to, Acklin et al., as well as to the presently claimed process. The examiner's unwarranted, theorizing speculation about the formation of cyanic acid with acetic acid as the sole acid is highly and unrealistically unlikely, not only because it contradicts the teaching of Acklin et al, but also because acetic acid is not only a weaker acid than formic acid, but **acetic acid is also a weaker acid than cyanic acid which it, therefore, cannot liberate from its salts** [1]. Even if in the case of slight equilibrium distortions one might speculate about the formation of minimal amounts of cyanic acid, the facts that (i) no formation of the any of the highly toxic, lachrimating kind of cyanic acid is being sensed, and (ii) the reaction in the case of the present invention goes forward with a yield in the order of 98%, bespeaks the presence of any cyanic acid, and certainly not any meaningful amount thereof.

For the above reasons, the applicant will not even try to deal any further with the examiner's speculations, except to point to its irrelevancy and contradictory nature to the baseline that has to be considered - that drawn between at one extreme the reference and at its other extreme the present invention. There is no room along that baseline for excursions into irrelevant asides.

The examiner stated in Paper No. 8 that a new translation of Acklin et al. has been ordered. No copy of that new translation was received by the undersigned. The examiner maintains that Acklin et al. mentions acetic acid in column 3, lines 27-41. If the examiner maintains that that mention of acetic acid means that it alone can liberate cyanic acid from its sal;ts, the examiner is seriously mistaken and has misread Acklin et al.

That reference discusses in Column 2, lines 39-54 that only certain protonic acids are sufficiently strong to liberate cyanic acid from its salts. Thus, it lists, mineral acids such as sulfuric acid, organic carbonic acids such as trichloroacetic acid, the acid strength of the acids used to correspond **at least** to that of formic acid (see footnote).

After line 55 and bridging over to column 3, Acklin et al. introduces the concept of a **further** "acidic agent" as a reaction-accelerating catalyst (for the second step of the reaction as an adjunct or alternative to heating), in addition to the acid used to liberate the

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[1] The pKa value of trichloroacetic acid, a very strong acid, is 0.70. The pKa value of cyanic acid is 3.47, and of formic acid is 3.77. Acetic acid is the weakest of them all at 4.75.

cyanic acid from its salts. That acidic agent is present only in a minimal, catalytic amount, and may be also a small excess of the acid that is used to liberate the cyanic acid from its salts. The examiner overlooks that part of Acklin et al. from line 55, and mistakenly relies only on the part of Acklin et al, from column 3, line 27. In column 3 lines 27-41 Acklin et al, refers to the presence of acetic acid, but Acklin et al. does that only in reference to the catalytic amount of the "acidic agent" **but <u>not</u> with reference to the acid used to liberate cyanic acid from its salts.** The "acidic agent" is only the infinitesimally small, the catalytic amount of additional acid, and therefore, when acetic acid is mentioned as a possible "acidic agent" that refers only to the small amount of additional acid catalyst for the second reaction step of Acklin et al, namely the reaction of the cyanic acid with the iminostilbene. Acetic acid may also be employed as a solvent, but in view of what has been stated in Acklin et al. earlier about the need for a stronger acid, it cannot be used to liberate cyanic acid from its salts,

There was a further rejection on the basis of alleged new matter. The rejection was responded to, and it is not clear whether that rejection was settled, or whether it is continuing. Therefore, the applicant prophylactically re-presents the earlier argument that was presented against it. The rejection objected to the inclusion in claim 8 of "aqueous alcohol." As it was pointed out during the prosecution, the original claim has specified "aqueous acetic acid" (which means acetic acid and water). The original claim also specified "with water or alcohol" (which means aqueous acetic acid either with more water or with just the original amount of water, and alcohol). Accordingly, either of these terms includes acetic acid, water and alcohol as one alternative to aqueous acetic acid with alcohol, i.e. acetic acid, water, and alcohol, i.e. aqueous alcohol. Hence the later added term of "aqueous alcohol" cannot, and does not represent any new matter., as water, acetic acid and alcohol were simultaneously present as ingredients of the original claims. The objected term can however be easily removed if the objection were to continue through the appeal.

Respectfully submitted

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I hereby certify that this correspondence is deposited with the U.S. Postal Service, addressed as above, on July 21, 2000

Cynthia A. Pilato

Appendix

8. A process for producing carbamazepine, which comprises reacting iminostilbene with an alkali cyanate in an acidic medium consisting of acetic acid, or a mixture of acetic acid with water, or with alcohol, or with an aqueous alcohol, and recovering the resulting carbamazepine.

2. The process of claim 8 wherein an aqueous acetic acid mixture is employed containing up to about 20% wt. water based on the mixture.

3. The process of claim 8, wherein an alcoholic acetic acid mixture is used containing up to about 10% wt. alcohol based on the mixture.

4. The process of claim 3, wherein the alcohol is methanol or ethanol.

5. The process of claim 8 wherein the alkali cyanate is gradually added directly to the reaction mixture of iminostilbene and acetic acid, or acetic acid mixture.

6. The process of claim 8 wherein the alkali cyanate is added in an aqueous solution.

7. The process of claim 8 wherein the alkali cyanate is sodium- or potassium cyanate.